RESULTS OF INTRAVENOUS IMMUNOGLOBULIN ADMINISTRATION IN CHILDHOOD ITP

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SUMMARY

One chronic and 10 acute ITP patients, admitted to the GATA Haydarpaşa Training Hospital Pediatric Clinic between February 1989 – February 1993 were treated by IVIG in doses of 0.5 g/kg for 5 days. Seven of the patients were female and 4 were male. The mean age was 4.8 years (2 months - 9 years). None of the patients revealed a maternal ITP history. Thrombocyte levels (mean 18,090 ± 7,634/mm^3) at admission rose sharply within 3 days and reached hemostatic levels on the 5th day (mean 231,272 ± 156,770/mm^3). These levels were checked on the 10th, 30th, 150th day and the average was found to be over 150,000/mm^3.

One patient (a 6 year old girl) who gave good response to initial IVIG diagnosed as acute ITP has shown recurrences. These attacks responded to IVIG treatment well and splenectomy was not needed. We observed no reccurences in the other 10 cases. No side effects relating to IVIG were reported.

IVIG therapy can be considered as a safe approach to childhood ITP, quickly restoring the hemostatic thrombocyte levels and thus preventing life-threatening complications such as intracranial hemorrhage in acute ITP and leading to favorable remission periods in chronic ITP.

Key Words: ITP, idiopathic thrombocytopenic purpura, intravenous immunoglobulin, IVIG.

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is an acquired disease that is characterized by thrombocytopenia, shortened thrombocyte life span, the presence of antithrombocyte factors in plasma and increased number of megakaryocytes in the bone marrow. Owing to its pathogenesis, the term immune thrombocytopenic purpura is more appropriate for this disease. All methods determining the presence of thrombocyte-autoantibody complexes yield positive results in nearly all ITP patients (1).

In the classic management of ITP, high dose corticosteroids are used. The disadvantages of this modality include, low response rates, a longer period required for the response, the high incidence of adverse effects, and high rates of relapses after discontinuation of the therapy (2, 3). Splenectomy, another way of treatment, is usually selected for chronic, adult patients who have massive bleedings. As splenectomy gives rise to irreversible immune deficiency, it is not recommended in childhood ITP. Cytotoxic drug therapy must be reserved as the last method. Thrombocyte concentrate infusions are of no use because of the high rate of destruction.

In recent years a new promising therapy modality, administration of intravenous immunoglobulin (IVIG), promoted thrombocyte counts to desired levels within 48-72 hours (4). This advantage makes the method superior to the other forms of therapy by preventing life threatening complications such as intracranial and massive mucosal bleedings seen early in the course (5, 6). By the administration of IVIG, the need for splenectomy was also reduced in chronic patients, especially in children since during childhood splenectomy is to be reserved because of its well-known risks (2, 7, 8).

The thrombocyte raising effect of IVIG in ITP can be explained by several mechanisms:

1. by interfering with the phagocytosis of antibody coated platelets in spleen via blockage of F_c receptors of the macrophages, 2. by depressing the T helper/supressor rate (9), 3. by reducing the number of natural killer cells, hence reducing immunoglobulin synthesis (10, 11). 4. by elimination of viral antigens

or immune complexes containing viral antigens from the surface of the platelets by its specific F_{ab} effect, 5. by enhancing the production of anti-idiotype antibodies againts anti-platelet antibodies.

The most important mechanism that causes the acute rise of thrombocyte levels is F_c receptor blockade. Reduction in immunoglobulin synthesis and the other complex immunologic modulations explain the late effects of IVIG (3).

Under the light of this current knowledge, we administered IVIG to our group of ITP patients, aiming to restore the thrombocyte levels quickly and gaining remission without splenectomy in chronic ITP.

MATERIALS AND METHOD

The patients encountered in his study were selected according to the following criteria:
1. presence of petechiae and purpurae, 2. thrombocyte count below 50.000/fL, 3. absence of abnormalities in the white and red cell series in peripheral blood, 4. absence of lymphadenomegaly and hepatosplenomegaly, 5. single and large thrombocytes, absence of thrombocyte aggregates in the peripheral blood smear, 6. increase in the number of megakaryocytic elements in bone marrow, while other series are normal and there is no infiltration of foreign cells, 7. elimination of other disorders that might cause thrombocytopenia.

Otherwise healthy acute and chronic ITP patients were selected, as none of them had a course of corticosteroid therapy, or even if the therapy was given, there had been no rise of thrombocyte levels over 50,000/mm^3 in the last 3 months. The IVIG therapy was delayed for 2 weeks if the patient had corticosteroid therapy. Also the cytotoxic drugs that have known effects on thrombocyte levels as Danazol and Vincristine were not used during therapy. Before the therapy was initiated, all patients were tested for diagnostic purposes and for follow-up. Hemogram, thrombocyte counts, bone marrow examination, anti-DNA, ANA, LE cell, serum quantittative immunoglobulin levels, C3, Direct Coombs test, bleeding time, clotting time, prothrombin time, routine blood chemistry, chest film, spleen and liver scintigraphy or abdominal ultrasonography were performed on each patient. All patients were hospitalized and given intravenous immunoglobulin in 5 consecutive days after the diagnosis was made. The dose was 0.5 g/kg/day by drip infusion at a rate of 1 ml/min. A thrombocyte count was repeated on the 3rd, 5th days and then the patients were followed as outpatients and the counts were repeated on the 10th and 30th days.

RESULTS

We retrospectively evaluated the results of 11 ITP patients (10 acute and one chronic) who were admitted to our clinic between February 1989 and February 1993. Four of them were male and 7 were female with avegare age being 4-8 years, ranging among 2 months old and 9 years old. The diagnoses were made by clinic and laboratory means. Identifiable causes of thrombocytopenia and bleeding disorders were excluded. Bone marrow examination revealed a normal marrow with a moderate increase in the number of megakaryocytes showing no maturation defect in all patients. All patients were treated by high doses of IVIG.

The platelet counts at the beginning of the therapy (mean 18,090 ± 7,634/mm^3) rose sharply within 72 hours and reached to hemostatic levels on the 5th day (mean 231,272 ± 156,770/mm^3). The thrombocyte levels were above 150,000/mm^3 on 10th, 30th and 150th days (mean 155,818 ± 50,617/mm^3). No relapses were observed in the acute ITP group. (Table I. Fig. 1).

A six-year-old female patient, who was accepted as acute ITP at the beginning, was readmitted with ecchymoses 360 days later. A second 5-day course of IVIG was given in the same dose. The patient was

Table I- Thrombocyte counts of cases

	DAYS					
CASE No:	1	3	5	10	30	150
1	20,000	110,000	642,000	712,000	150,000	140,000
2	17,000	27,000	294,000	302,000	563,000	203,000
3	22,000	51,000	156,000	263,000	151,000	123,000
4	19,000	67,000	78,000	92,000	104,000	189,000
5	36,000	63,000	82,000	101,000	194,000	139,000
6	21,000	58,000	238,000	281,000	201,000	152,000
7	23.000	63,000	327,000	452,000	249,000	172,000
8	21,000	64,000	298,000	207,000	237,000	218,000
9	12,000	83,000	118,000	251,000	142,000	62,000
10	21,000	52,000	99,000	212,000	193,000	123,000
MEAN	21,200	63,800	233,200	287,300	218,400	152,100

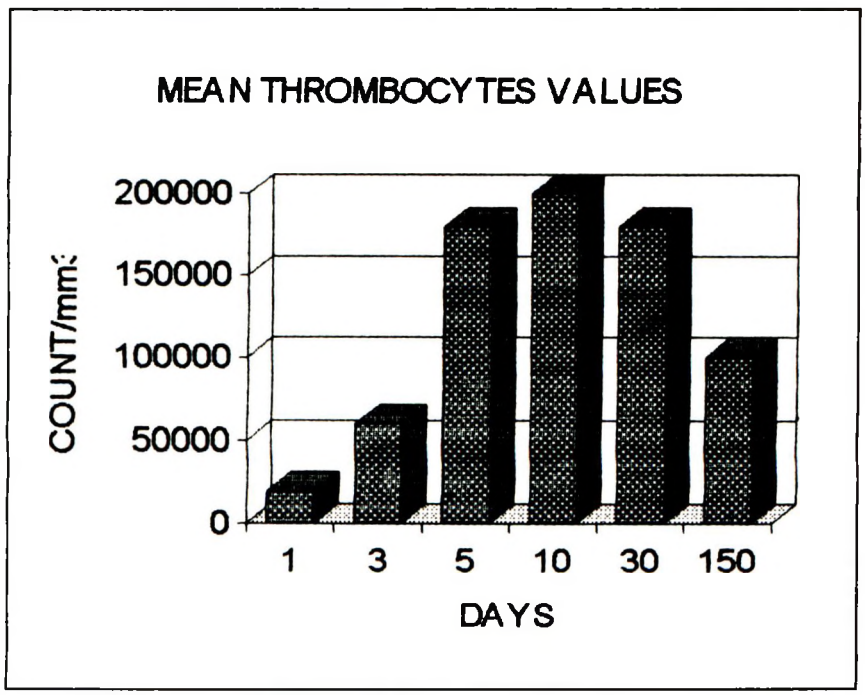

Fig 1. The thrombocyte response to IVIG

discharged uneventfully. A second relapse occurred 150 days later, also well-responding to IVIG. The patient was then put on 1g/kg IVIG infusions monthly. We did not consider splenectomy and achieved 30-60 days of remissions with IVIG.

The difference between the pretreatment and posttreatment thrombocyte levels were significant ($p<0.001$). The degree of the initial thrombocyte levels did not influence the ultimate response. Only 5th day and 10th day thrombocyte levels correlated positively. Age or sex of the patients did not effect the outcome.

We observed no side effects due to IVIG. Except for the minor skin and mucosal bleedings present at the admittance, no further bleeding or life threatening complications were encountered.

DISCUSSION

In recent years, IVIG is being used widely in acute or chronic forms of childhood and adult ITP. Fast, dramatic rises of thrombocyte levels are observed after the adminisration of IVIG (5). Nevertheless, the duration of response, optimal doses and the cure rates are still debatable. We tried to seek answers to these common questions although we had a small group of patients.
In acute and chronic ITP, steroids, plasmapheresis, splenectomy and some cytotoxic drugs were used and good results comparable with IVIG have been observed (2, 8). The question here is, when and whom to give IVIG and what makes IVIG superior to the other methods.

The first step in ITP therapy is corticosteroids (12). Eighty percent of children who have not recovered spontaneously, responded to this therapy. Besides the well-known immunosuppressive effect of steroids, the thrombocyte-raising effect may be delayed in the following 15 days. Because the impending irreversible immune deficiency enhances the risk of infection, splenectomy must be deferred in children who have a chance of spontoneous remission. We preferred to treat our patients with IVIG because the patients are at risk of life-threatening hemorrhage when left to spontaneous remission and it is possible to obtain hemostatic thrombocyte levels with IVIG within 1 or 2 days without any side-effects, As seen in table I, the thrombocyte levels of patients receiving IVIG have reached hemostatic levels in the first three days of the therapy. Acutely bleeding patients or patients who must be prepared to an urgent operation are good candidates for IVIG treatment. In pregnant women, long term corticosteroid therapy may enhance the risk of eclampsy and splenectomy increases fetal mortality 30 percent.

In our study, except one case, none of the patients needed maintenance therapy and no relapses were reported up to now. In a report, IVIG was compared with corticosteroids in acute ITP and 60-100 days of treatment-free periods were obtained in the IVIG group. These results are also consistent with our study (2, 13).

Conflicting results are reported in chronic ITP. In some cases, refractoriness to IVIG was encountered after a period. The mechanism of refractoriness is not well known, as are the long term effects of IVIG. The hypothesis that can be valid here is, IVIG may promote antibody synthesis in some patients while suppressing it in others. It is shown that when IVIG is used in conjunction with plasmapheresis, a favorable response can be achieved once more (14). This mechanism may explain the shortening of the remission period as deserved despite IVIG administration in one case. Plasmapheresis was not applied to the patient since we have only one chronic case, we hold off the debate of IVIG use in chronic ITP.

As a result, we obtained good responses in our acute ITP patients, compatible with other reports.

REFERENCES

1. *Beardsley DS, Spiegel JE, Jacobs MM, Handin RI, Luz SE. Platelet membrane glycoprotein IIIa contains target antigens that binds anti-platelet antibodies in immune thrombocytopenias. J Clin Invest 1984;74:1701-1707.*
2. *Imbach P, Wagner HP, Berchtold W. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. Lancet 1985;2:464-468.*
3. *Bussell JB, Kimberley RP, Inman RD. Intravenous gamma globulin treatment of chronic idiopathic thrombocytopenic purpura. Blood 1983;62:480-486.*
4. *Imbach P, Barandun S, d'Apuzzo V. High dose intravenous gamma globulin for idiopathic thrombocytopenic purpura in childhood. Lancet 1981;1:1228-1231.*
5. *Fehr J, Hoffmann V, Kappeler U. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gamma globulin. N Eng J Med 1982;306:1254-1258.*
6. *Imholz B, Imbach P, Baumgartner C, et al. Intravenous immunoglobulin %IVIgG' for previously treated acute or for chronic idiopathic thrombocytopenic purpura in childhood a prospective multicenter study. Lut 1988;56:63-68.*
7. *Bussell JB, Goldman A, Imbach P, Schulman I. Treatment of acute idiopathic thrombocytopenia of childhood with intravenous infusions of gammaglobulin. J Pediatr 1985;106:886-890.*
8. *Bussell JB, Schulman I, Hilgartner MW, Brandun S. 'Intravenous use of gamma globulin in the treatment of chronic immune thrombocytopenic purpura as a mean to defer splenectomy. J Pediatr 1983;103:651-654.*
9. *Tsubakio T, Kuruta Y, Katagiri S. Alteration of T cell subsets and immunoglobulin synthesis in vitro during high dose gamma globulin therapy in patient with ITP. Clin Exp Immunol 1983;53:697-702.*
10. *Winiarsky J, Kreuger A, Ejderhamm J, Holm G. High dose intravenous IgG reduces platelet associated immunoglobulins and complement in ITP. Scand J Haematol 1983;31:342-348.*
11. *Englehard D, Warner JL, Kapoor N, Good RA. Effect of intravenous immune globulin on natural killer cell activity. Possible association with autoimmune neutropenia and idiopathic thrombocytopenia. J Pediatr 1986;108:77-81.*
12. *McMillan R. Chronic idiopatic thrombocytopenic purpura. N England J Med 1981. 304:1135-1147.*
13. *Salama A, Mueller-Eckhardt C, Kiefel V. Effect of intravenous immunoglobulin in immune thrombocytopenia. Lancet 1983;2:193-195.*
14. *Bussell JB, Saal S, Gordon B. Combined plasma exchange and intravenous gamma globulin in the treatment of patients with refractory immune thrombocytopenic purpura. Transfusion 1988;28:38-41.*